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SYNTHESIS OF NATURAL PRODUCTS VIA TERTIARY AZIDES I
2-ALKYL AND CIS 2,6 ALKYLPIPERIDINE ALKALOIDS

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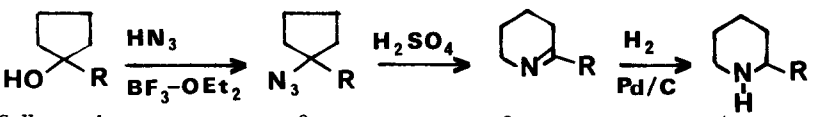
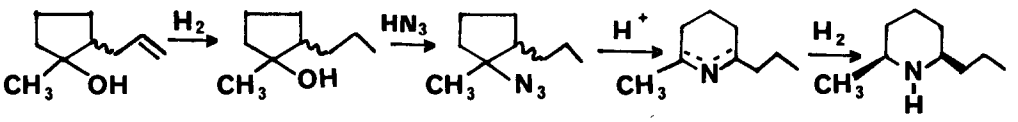
By action of the N_3H/BF_3-OEt_2 reagent on trisubstituted olefins or tertiary alcohols, a certain number of tertiary azides have been synthesized (I,2,3). The acid-catalysed breakdown of cyclopentane tertiary azides provides α-substituted piperideines in good yield. The hereby related work is the application of this reaction to the synthesis of piperidine alkaloids : γ-coniceine , (±) coniine and (±) dihydropinidine (and similar compounds). 1-Hydroxy n-propyl cyclopentane 1 , upon treatment with the above reagent, leads to 1-azido n-propylcyclopentane 2 in 71% yield (distilled) , bp $_{15}$: 71-72° , $n_D^{22°}$: 1,4670 , IR (νN_3) 2100 cm^{-1}, NMR : t 0,95 ppm (J=7 Hz) , MS : M^+ 153 , m/e 125,110 . At 0° , 2 undergoes an acid-catalysed breakdown in $CHCl_3$ with H_2SO_4 and , after basification , leads to colourless oil in 93% yield (distilled) . This oil is identified by its physical and chemical data as α-propylpiperideine or γ-coniceine 3 (4). By hydrogenation (Pd/C 10%), 3 is transformed in 95% yield into 2-propylpiperidine 8 or (±) coniine identical with an authentic sample .



R = n C_3H_7	1	2	3	4
CH_3	5	6	7	8
n C_4H_9	9	10	11	12

The overall yield is 63% and , in a similar manner , 1-alkyl cyclopentanols 5 and 9 provide 2-alkyl piperidines 8 and 12 respectively in good yield too. The reaction was extended to the synthesis of 2,6-disubstituted piperidine alkaloids starting from 2-alkyl 1-methyl cyclopentanols (±) Dihydropinidine 17 was obtained following the undermentioned path. 2-allyl cyclopentanone treated by methylmagnesium iodide in ether gives 2-allyl 1-methyl cyclopentanol 13,catalytic hydrogenation of which provides 2-propyl 1-methyl cyclopentanol I4 , bp $_{18}$: 82-83° , mixture of trans Me/C_3H_7 61% , cis 39% (VPC and NMR) , By traitment of I4 with N_3H/BF_3-OEt_2 in CH_2Cl_2 (0°,30 min) 2-propyl 1-azido cyclopentane 15 is obtained : $C_9H_{17}N$, mixture of trans Me/C_3H_7 37% , cis 63% (VPC and NMR) , IR (νN_3) 2095 cm^{-1} , MS : M^+ 167. Its acid-catalysed breakdown leads to 16 : IR ($\nu C{=}N$) 1660 cm^{-1} . The crude mixture is hydrogenated (Pd/C 10%) and provides 17 which is identified as (±) dihydropinidine I7 on the basis of physical data (5).



13 14 15 16 17

The overall yield is about 60% (13→17) , whereas HILL's synthesis by N-acyl lactam rearrangement afforded only 15% yield (5) . Thus , the acid-catalysed breakdown of cyclopentane tertiary azides permits the access to a series of 2-substituted and 2,6-disubstituted piperidine alkaloids with the best yields known up to now (6) .

REFERENCES

(1) A.ASTIER , thèse Doctorat es Sciences , Paris XI Orsay Juin I976.

(2) A.ASTIER, A.PANCRAZI and Q.KHUONG-HUU, Tetrahedron I978 , in press (part one).

(3) A.ASTIER, A.PANCRAZI and Q.KHUONG-HUU, Tetrahedron I978 , in press (part two).

(4) R.H.F. MANSKE , The Alkaloids , vol XI , Acad. Press , N.Y .

(5) R.K. HILL and T.YURI , Tetrahedron , 33 , 1569 (1977) .

(6) DOAN-HUYNH-DONG ,Thèse 3° cycle , Paris Orsay 1977 .

E. LEETE and R.A. CARVER , J. Org. Chem. , 40 , 2151 (1975) .